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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,331	12/18/2001	Andrew A. Young	030639.0031,UTL1	2765

7590 01/29/2003

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	17

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,331	YOUNG ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' response filed 21 November 2002 (paper No. 12) as to amendment of claim 1, addition of new claims 9-13, and request for extension of time of one-month have bee entered. The following Office action is applicable to the pending claims 1-13.

The declaration filed on November 21,2002 under 37 CFR 1.131 is sufficient to overcome US Pat. No. 6376549.

Note that the grounds of objection and/or rejection not explicitly stated and/or set forth below are withdrawn.

Claim/Objections

The disclosure is objected to because of the following informalities:

Claim 11 recites "in dosage unit form" wherein "a" is missing before "dosage".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7-8 and 9-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for conjugating PEG polymer to the claimed exendin-4 peptide and use of the synthetic exendin peptides (non-conjugated to PEG) for suppressing or/and lowering glucagon secretion in a patient having Type 2 diabetes, does not reasonably

provide enablement for using the *PEG-modified* exendin-4 conjugates to treat glucagonoma syndrome that is characterized by a necrolytic migratory erythematous rash, *i.e.*, necrolytic migratory erythema (see Bloom, S. R. *et al.* (1987) *Am. J. Med.* 82, (suppl 5B) 25-36). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant application is directed to a method of lowering plasma glucagon and treating disease states characterized by abnormally high blood glucagon levels, by administering to patients a pharmaceutical composition comprising the PEG-modified exendin-4. However, the specification does not provide working example, a description as to treatment of the disorders glucagonoma and glucagonoma-related necrolytic migratory erythema employing the EG-modified exendin-4.

The application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The nature of the invention/The scope of the claims:

Claim 1 sets forth a method of lowering plasma glucagon in a subject, comprising administering the modified exendin to a subject, and claims 2 and 3 set forth that the said subject has glucagonoma-related necrolytic migratory erythema or glucagonoma, respectively.

As mentioned above, the claims as written are directed to use of the PEG-modified exendin-4 peptides as a pharmaceutics to treat the glucagonoma and related disorders. The specification establishes the method of preparation exendin and the PEG-modified exendin mediated peptides, shows a decrease of plasma glucagon mediated by the peptides, and sets forth example for effect of the exendin peptide on glucagon secretion in patients with type II diabetes. However, the specification is silent as to a therapeutic relation of lowering glucagon secretion by the PEG-modified exendin to the disease states: glucagonoma and glucagonoma-related necrolytic migratory erythema. A sufficient description of such the relation is necessary for the skilled artisan to practice the invention. Yet, the specification does not provide working examples and guidance for treatment of the disorders treated by the PEG-modified exendin. Applicant is in possession of treating type II diabetes by the exendin-4 by the mechanism of lowering glucagon in the subject, but not in possession of treating glucagonoma and necrolytic migratory erythema by PEG-modified exendin-4 or analog thereof.

The specification sets forth that PEG molecules (≤ 3) are covalently linked to exendin-4 (see page 64, lines 15-19), whereas claims 7 and 8 set forth that one or more PED polymers (note the number of PEG molecules herein can be very large) are linked to modified exendin which would encompass those have formerly been PGE-conjugated. As a result, the size of the exendin-PED would be exceedingly large due to such the "*multiple PEG-modifications*". In addition, since claim 8 sets forth that one or more PEG polymers (without the upper limit) are linked to the

exendin-4. This would unpredictably magnify the size of the PEG-exendin, which raise problem with regard to solubility of the produced PEG-exendin complex in biological environment when formulated and administered, absent factual indicia to the contrary. In comparison of the limitation set forth by the claims with the disclosure set firth by the specification, the scope of claims is so broad that the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

(2) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Because, as mentioned in the foregoing statement, the combination number of the PEG-exendin conjugates (genus) as claimed is large and the conjugates are highly variant (see the PEG-modified exendin is additionally further linked to PEG polymers, *in reference to* claim 7), and because each variant conjugate has different/distinct water-solubility (see page 10, lines 1-14) that determines pharmaceutical efficacy of the PEG-exendin applicable to the disorders or diseases, absent factual indicia to the contrary, one of skilled artisan would be required to perform undue experimentation in order to screen, test for and characterize one of each conjugate variants, including solubility, biological stability (related to clearance by the kidney (see example 3) as well as pharmaceutical efficacy.

On the other hand, different disorders and diseases require different therapeutic procedures and protocols as well as doses and forms of pharmaceutics. Even for treatment of a given disorder, parameters e.g. dose and administering time for achieving reasonable therapeutic effect of the exendin peptide is needed to be determined (see the bell curves of dose-dependent

[figure 4(d)] and plasma concentration-dependent anti-diabetic effect of the exendin [figure 4(f)], as well as time-dependent fashion [figure 4(b)] (see *Parkes, D. G. et al.* (2001) *Metabolism* 50, 583-589). Since the above-mentioned therapeutic parameters are the modified PEG dependent, the specification needs to provide sufficient guidance to support the enablement.

(3) The unpredictability of the art:

Because the claimed method involves highly variant PEG-modified exendin conjugates which is the subject matter of the current invention, outcome of administering the composition comprising the PEG-modified exendin-4 to a subject having glucagonoma syndrome or glucagonoma associated necrolytic migratory erythema is unpredictable in the absence of factual indicia to the contrary.

(4) The quantity of experimentation necessary:

In the absence of working examples as to the PEG-modified exendin variants and the undetermined therapeutic parameters referring to each variant, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Because of the reasons forgoing, the quantity of experimentation would be large and of unpredictability. The skilled artisan would be required to carry out a large quantity of search for water soluble as well as biologically stable PEG-modified exendin variant(s), and to establish a suitable animal model so as to determine therapeutic parameters for treatment of the disorders. For the instance, biological half-life of the antidiabetic composition needs to be determined prior to administering the composition; the clinical utility and development of the antidiabetic composition has been frustrated, at least in

part, by its short half-life in man and the need for continuous or frequent administration (see Figure 4(f), pages 583 and 586, Parkes *et al.*).

(5) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to an unpredictable number of the PEG-exendin conjugate variants. In view of the preceding factors (1-4), the level of skill in this art is high and requires at least a protein-engineer, an endocrinologist and a cell biologist at Ph.D. level with several years of experience in peptide chemistry as well as knowledge in peptide synthesis, endocrinology, oncology, and molecular biology; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable.

One of key parameters affecting the exendin therapeutic effect is the biological half-time *in vivo*. Drucker D. J. *et al.* (*Diabetes* (1998) 47, 159-169) teach that novel glucagon-like peptides, *i.e.*, exendin peptides, are more potent than native glucagon-like peptide 1 (GLP-1) and has higher biological stability than GLP-1 *in vivo* as to therapeutic application (see the left column of page 164 and the second paragraph). This does not, however, necessarily reflect the exendin peptide or PEG modified thereof is stable enough being resistant to proteolysis during administration. This is evidenced by the Parkes *et al.* demonstration that plasma concentration (as to stability) of exendin peptide is highly dependent upon time and mean of administering (see Figure 4(a) and 4(d)).

The specification describes biological half-time related "clearance by the kidney" of the unmodified exendin-4 peptide (see example 3,and Figures 5 and 6). However, the specification fails to teach the same with regard to the **PEG-modified** exendin-4 peptide.

In light of the above-mentioned variant PEG-modified exendin variants, unpredictability of biological half-life and solubility of the variants when administered, pre-determination of several therapeutic parameters, *e.g.*, does, time, mean of administering, there is undue experimentation because of variableness in prediction of outcome that is not addressed by the instant application teaching, examples and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Response to the rejection under 35 USC 112, the first paragraph

The response field 21 November 2002 asserts that examples 4 and 5 teach exendin-4 decreases glucagon secretion in diabetic rats and in patients suffering Type II diabetes, respectively (see page 11), asserts that the specification at page 8, lines 20-25, teaches, in general, the treatment of hyperglucgonemia and conditions including but not limited to necrolytic migratory erythema, and infers that there is no reason to doubt that the skilled artisan would be able to practice the full scope of the claimed invention (see page 12, the first paragraph). The applicant's argument is unpersuasive because the specification neither teaches/provides working examples for the treatment of glucagonoma and necrolytic migratory erythema by administering the composition comprising the PEG-conjugated exendin-4, nor for lowering glucagon *in vivo* (a animal model) by the PEG-modified exendin-4.

The response discusses therapeutic background of glucagonoma and glucagonoma-related necrolytic migratory erythema, and asserts that the specification describes conditions as to glucagonostatic agent, *e.g.*, the compounds of the claimed methods has ability to suppress glucagon secretion (see pages 13-14). Note that nowhere in the specification has guidance been

provided as to reduction of plasma glucagon level by the PEG-modified exendin-4 that is the subject compound of the current application. Thus, the applicant's argument is not persuasive.

The response discusses means of administering the claimed exendin analog to the subject for treatment of glucagonoma and glucagonoma-related necrolytic migratory erythema, and infers that "the specification provides adequate guidance for practice of the invention, which exact methods employed are determined by those skilled in the art, *e.g.*, clinicians employing the methods during treatment of their patients" (see page 14). The argument is unpersuasive. The current application is directed to a method of suppressing or/and lowering glucagon in a subject who suffering glucagonoma, necrolytic migratory erythema or Type II diabetes comprising administering to the subject the **PEG-modified** exendin-4. The specification does not provide guidance or/and teaching as to this regard. Instead, the specification teaches unmodified exendin-4 for reducing glucagon in diabetic rats (see example 4) and in patients with Type II diabetes (see example 5).

Also, the response discusses the issue regarding unpredictability of PEG-modified exendin variants (see pages 14-16), and asserts that the claimed methods all relate to "lowering plasma glucagon" and "applicants provide multiple working examples as well as other description" (see page 16, the first paragraph). The applicants' argument is not persuasive because the claimed methods are based on use of the PEG-modified exendin-4 peptide analog. Since the current application claims a therapeutic composition comprising the exendin, appropriate animal model(s) is necessary. Yet, the specification provides no working examples as to lowering glucagon using the PEG-modified exendin-4 in the animal model, rather the specification provides the same using unmodified exendin-4 (see examples 4 and 5).

Further, the response asserts that the Examiner limits the claims to preferred embodiments of the invention when construing their scope for reasons of comparison with the rest of the specification (see page 16, the second paragraph) and discusses the issue regarding the scope of claim being comparable to the scope of the current specification.

As stated in the rejection *supra*, claims 7 and 8 set forth that one or more PED polymers that sets up no upper limit, thus, the number of PEG molecules to be linked to the exendin-4 would be exceedingly large). Moreover, these PEG polymers are linked to modified exendin which have been PGE-modified. In consequence, the resultant products, *i.e.*, exendin-PED complex would be large depending on a PEG type used which has fidderent molecular weight (*e.g.*, 500 to 20000 daltons) and unpredictable. Such the complex would not be invariable and would create a problem as to solubility in biological environment when formulated and administered, absent factual indicia to the contrary. The specification sets forth the size of the PEG ranges from a molecular weight of 500 to 20,000 (see page 64, lines 17-19, and claim 8). Because the specification does not teaches PEG-conjugation to the PEG-modified exendin peptide, and because the claims set forth much complex PEG-modified product than does the specification, the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (amended) is indefinite as to the difference between exendin and exendin agonist (exendin is an exendin agonist and a modified exendin is also a modified exendin agonist). The comments in the response have been considered (pages 18-19) but do not *per se* define the terminology as being that which applicant asserts in the response. Also, claim 1 is indefinite as being an improper Markush group. Markush-type claim requires "selected from the group consisting of" members or species (see MPEP 803.2). Also, claim 1 is indefinite in "selected from ... and..." wherein "and" renders the claim indefinite; suggest "or" instead. See also claim 9. The dependent claims are also rejected. In addition, claim 1 is unclear as to "modified exendin" and "modified exendin agonist"; to what are the modification compared? and, to what kind of modification the claim refers. Note that modification can be divided into 4 categories: physical, chemical, enzymatic and genetic modification, wherein, physical modification refers to, *e.g.*, multimerization and aggregation; enzymatic modification refers to, *e.g.*, proteolytic cleavage of exendin peptide; chemical modification refers to, *e.g.*, an amino acid side-chain modification; and genetic modification regards, *e.g.*, mutagenesis of exendin peptide.

Claim 6 recites "any of claims 1-3 or 4..."; does the recitation refer to four methods of claims in the precedence to the claim 6? Suggest "any one of claims 1-4".

Claim 7 is indefinite in the recitation "modified exendin ...is linked to one or more polyethylene glycol (PEG) polymer" because the recitation is unclear as to (i) whether or not

"modified" refer to PEG modification (*i.e.*, PEGylation) of the exendin peptide; (ii) given the modified exendin herein is PEGylated peptide, whether or not the PEGylated exendin is further subject to PEG conjugation, and whether or not the PEGylated exendin is further conjugated to PEG polymer(s) by a *PEG-PEG* linkage or by a *peptide-PEG* linkage; and (iii) what is chemical nature of the "modified exendin" that is not modified by PEGylation?

Claim 10 recites "... at least one of an exendin, ..."; the recitation is vague due to missing the nexus between "at least one of" and "an exendin, ...".

Response to the rejection under 35 USC 112, the second paragraph

The response filed 21 November 2002 discusses the issue regarding the recitation "...any of claims 1-3 or 4..." in claims 6 and 7. The argument is not persuasive because the recitation is not apparent as to whether or not the recited "4" refers to four methods from claims 1-5. The claim language would be clear by reciting "the method of any one of claims 1-4".

Also, the response asserts that claims 7 and 8 are read in light of the specification, one of ordinary skill in the art is able to determine the nature and extent of conjugation best suited for the claimed methods of claims 7 and 8 (see page 21-22). The applicant's argument is unpersuasive. Claim 7 is indefinite in the recitation "modified exendin ...is linked to one or more polyethylene glycol (PEG) polymer" because the recitation is unclear as to (i) what is chemical nature of the moiety that is not PEG linked to the exendin peptide; and (ii) given "modified" refer to PEGylation and the modified exendin refers to as the PEGylated peptide, whether or not the PEGylated exendin (*i.e.*, PEG-modified exendin) is further subject to PEGylation, and

whether or not the PEGylated exendin is further conjugated to PEG polymer(s) by a *PEG-PEG* linkage or by a *peptide-PEG* linkage.

The specification though defines (i) PEG modification of therapeutic peptides and proteins in general (see page 7, lines 13-14) and (ii) the modified exendin having an exendin peptide linked to one or more PEG polymer, and provides information regarding conjugation of PEG to non-PEGylated exendin peptide in general (see pages 49-50), the specification does not provide teaching and guidance as to how or/and why PEGylated exendin peptide is subject to further PEG-modification and biological significance thereof. Therefore, in light of the specification, the skilled artisan will not readily understand the metes and bounds of the claimed invention. The claim is hence indefinite.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-6 and 9-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Eng, J. (US Pat. No. 5424286, newly cited).

Eng teaches that glucagon-like insulinotropic peptide (GLIP) significantly lowers the plasma concentrations of insulin and glucagon (see column 1, lines 59-62), and teaches that, like GLIP, exendin-4 acts as an insulinotropic agent. Thus, lowering plasma glucagon in a subject is inherent in the patent. The Eng's teaching is applied to claims 1, 4-6 and 9-10 of the instant application. Since glucagonoma and necrolytic migratory erythema are associated with elevated plasma glucagon level, claims 2 and 3 are also included in the rejection.

Eng teaches exendin-4 and methods for the treatment of diabetes mellitus and the prevention of hyperglycemia using exendin-4 and derivatives (see abstract), as applied to claims 11-12 of the current application. Note that because non-insulin dependent diabetes, mellitus, *i.e.*, type II diabetes, is marked by hyperglycemia which is prevented by administration of exendin-4 peptide (see column 2, lines 37-40); thus, claim 13 is anticipated by the patent as well.

Thus, the Eng Patent anticipates claims 1-6 and 9-13 of the instant application.

Claims 1-6 and 9-13 are rejected under 35 U.S.C. 102(a) as being anticipated by the reference (*Marketletter*, Published on 24 August 1998, newly cited).

The reference discloses a process of using exendin-4 to inhibit glucagon secretion and clinically treat Type II diabetes patient. The reference disclosure meets all the limitation of claims 1, 4-6 and 9-13 of the instant application. Because glucagonoma and necrolytic migratory erythema are featured by abnormally elevated glucagon, and because the reference teach exendin-4 suppresses glucagon *via* inhibiting glucagon secretion, the reference anticipates claims 2 and 3 as well.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a). Note that this a new ground of the rejection.

Claims 1 and 4-8 are rejected under 35 U.S.C. 103(a) as being obvious over the reference (*Marketletter*, 24 August 1998, newly cited), taken with Drucker, D. J. (US Pat. No. 6051557), Beeley, N. *et al.* (WO9830231) and Frank, D. *et al.* (US Pat. No. 4179397).

The *Marketletter* discloses a process of using exendin-4 to inhibit glucagon secretion and clinically treat Type II diabetes patient. The reference disclosure meets all the limitation of claims 1-6 and 9-13 of the instant application.

The *Marketletter*, however, does not teach conjugation of PEG polymer to exendin or exendin derivatives.

Drucker *et al.* teach conjugate of PEG homopolymers to glucagon-related peptide (GLP), which is structurally and functionally related to exendin in order to enhance solubility of the peptide in aqueous solution, increase stability in storage, reduce immunogenicity, increase the peptide resistance to proteolytic degradation, and increase *in vivo* half life of the peptide (see column 19). Drucker *et al.* teach covalent linkage of peptide hormone to one or more polymers; Of the polymers, PEG homopolymer is particularly preferred (see column 19, lines 26-28 and 44-45). The Drucker *et al.* teaching therefore meets the limitation of Claim 7 of the instant application.

Drucker *et al.* do not teach the process of the covalent conjugation of exendin to PEG polymers.

Beeley *et al.*, however, teach covalent modification of amino acid residues of exendin peptide, including Glycine N-modification, *e.g.*, N-alkylglycine (see page 17 and 21) or tert-butylglycine (see page 22 and 24), and covalent conjugation of biopolymer(s) to the peptide terminus (C-terminus) (see formula II and pages 19-21), as applied to Claim 7 of the instant application. Beeley *et al.* teach the exendin agonist is exendin-4 peptide (see page 11, line 19 and claims 1, 17, 21 and 25), as applied to Claims 4-5 of the instant application. Beeley *et al.* further teach that the pharmaceutical composition comprising the exendin peptide is administered to a human subject with a therapeutically effective amount (see patent claim 27), as applied to claim 1, 6 and 9-13 of the instant application.

Frank *et al.* teach that covalent conjugation of polypeptides and peptide hormone, *e.g.*, insulin to polyethylene glycol (PEG) having a molecular weight of 500 to 20,000 daltons (see

claims 1 and 14-23 and columns 2-3), as applied to Claim 8 of the instant application. Please note that the Frank *et al.* reference has been incorporated by Drucker *et al.*

One of ordinary skill in the art would have combined the teachings of the above references to arrive at the current invention, because the *Marketletter* teaches a method of reducing glucagon level by exendin-4 and treating type II diabetes by administering to a patient the exendin-4, both Beely and Frank teach the conjugation of PEG to exendin peptide, and Drucker teaches the biological favorableness of the PEG-conjugated exendin. When combined, there also are the following advantages: (***a***) exendin agonist, and chemically modified exendin (see Formulas I and II at pages 16-23) that mimics the naturally-occurring exendin (see page 9, line 9-12) but offers even better pharmaceutical activity than unmodified exendin (compare Figure 4 to Figure 5), as taught by Beeley *et al.*; (***b***) PEG-conjugated exendin has enhanced solubility in aqueous solution, increased stability in storage, reduced immunogenicity, increased the peptide resistance to proteolytic degradation, and prolonged *in vivo* half life (see column 19), as taught by Drucker *et al.* and (*c*) PEG having a MW 500-20,000 daltons offers a physiological active non-immunogenic as well as water-soluble polypeptide composition, as taught by Frank *et al.* (see abstract and Claims 1 and 14-23).

Given the above motivation, one of ordinary skill in the art would have combined the teaching of the above references, and would have resulted in pharmaceutical composition comprising the PEG-exendin compounds for lowering plasma glucagon, and thereby treating disorders or diseases associated with abnormally elevated plasma glucagon level and treating Type II diabetes employing exendin and analog thereof as claimed in the current application.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

SWL

January 23, 2003

Christopher S. F. Low

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